

## DERIVATIVE WEIGHTED ACTIVE INSULIN CONTROL ALGORITHMS AND TRIALS

J. Geoffrey Chase<sup>1</sup>, Geoffrey M. Shaw<sup>2</sup>, Carmen V. Doran<sup>3</sup>, Nicolas H. Hudson<sup>3</sup> and Katherine T. Moorhead<sup>3</sup>

*Dept of Mechanical Engineering, University of Canterbury  
Dept of Intensive Care Medicine, Christchurch Hospital*

**Abstract:** Close control of blood glucose levels significantly reduces vascular complications in diabetes. Heavy derivative controllers utilising the data density available from emerging biosensors are developed to provide tight, optimal control of elevated blood glucose levels. A two-compartment human model is developed for intravenous infusion from physiologically verified subcutaneous infusion models to enable a first of its kind, proof-of-concept clinical trial. Results show tight control with very similar performance to modelled behaviour and strong correlation between modelled insulin used versus the amounts used in clinical trials to validate the models and methods developed. *Copyright © 2003 IFAC*

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### 1. INTRODUCTION

Diabetes is a disorder of the metabolism whereby insufficient insulin is produced by the beta cells, and as such blood glucose cannot be transported out of the blood. Lack of insulin results in blood glucose levels remaining dangerously high, which untreated over time leads to costly complications, including kidney failure, blindness, nerve damage, heart attack and stroke. Over 120 million people are affected by diabetes worldwide, and this number is expected to rise to 300 million by the year 2025 (Thomsen et al., 2001).

After a meal blood glucose rises over the basal level, which is approximately 4.5mmol/L for a normal individual, and typically takes two-three hours to return to basal levels. Type 1 diabetic individuals see high blood glucose levels which do not fall without exogenous insulin, while Type 2 diabetic individuals fall towards basal levels very slowly and may require exogenous insulin in severe cases. Type 1 and Type 2 diabetic individuals typically start with elevated basal blood glucose levels, as a result of their condition.

insulin into the subcutaneous tissue as required. Using a glucose monitoring system and an insulin pump or syringe injections, all current treatments are performed manually. Therefore, diabetic individuals must monitor food intake and daily activity to maintain acceptable blood glucose levels.

For ease of management, many subjects elect to maintain strict routines and diets to minimize manual monitoring and injection, reducing intervention and difficulty. This regime can lead to severe limitation of the subjects' lifestyle and is prone to human error. As a result, many diabetic individuals have difficulty maintaining tight blood glucose control, resulting in regular exposure to elevated blood glucose levels.

Hence, automated treatment promises better, more consistent control of blood glucose and an associated reduction in diabetes related complications. Existing insulin pumps, and emerging non-invasive and semi-invasive glucose monitoring systems may be easily interconnected to realise a closed loop system. Ultimately, the control unit should be able to automate 90 – 95% of a diabetic's day-to-day insulin care, freeing the patient from the anxieties and stress of constantly monitoring their blood glucose system behaviour, allowing them to lead more "normal" lives. Therefore, the goal is to control the essential dynamics rather than all of the dynamics and exceptional behaviours.

<sup>1</sup> Sr. Lecturer, <sup>2</sup> Consultant ICU

<sup>3</sup> Research Assistant

Current treatment methods involve regular point monitoring of the plasma glucose level and injecting

Years of research on modelling and managing diabetes have led to no shortage of theoretical automated solutions (e.g. Ollerton, 1989; Kienetz and Yoneyama, 1993; Fisher, 1991; Furler et al, 1985). However, due to either the complexity of the proposed implementation, models that are not physiologically verified, or lack of required data these solutions have not been trialled. Several researchers have examined the analysis and automation of insulin administration as reviewed by Lehman and Deutsch (1996). In each case, the focus has been on controlling absolute blood glucose excursion rather than the shape of the glucose curve as with heavy derivative control (Chase et al, 2002).

Prior work in tightly controlling elevated blood glucose levels using heavy derivative control employed a physiologically verified three compartment model based on the work of Bergman et al (1985). Performance was shown to improve with decreased sensor lag and sampling period and the controlled solution outperformed the normal human body at a sample period of 1 minute (Lam et al, 2002). The primary feature of derivative weighted control is the focus on controlling the shape of the blood glucose curve rather than the absolute magnitude of blood glucose. This approach adds robustness because it can account for varying rates of glucose absorption and other patient specific behaviours, as well as some other modelling errors.

The research presented here develops this heavy derivative control approach to a proof-of-concept clinical trial with Intensive Care Unit (ICU) patients. This clinical trial is the first of its kind, to the best of the authors' knowledge, to test a feedback control algorithm for tight glucose regulation. The 3-compartment model is adapted to a 2-compartment model for testing ICU patients who receive the insulin intravenously. Results are compared to predicted values to verify the modelling methods and overall approach to controlling blood glucose.

## 2. CLINICAL TRIAL METHOD

The proof-of-concept clinical trials conducted effectively simulate a true feedback control system with a 15-minute sampling period, which works well and represents a realistic level of system performance (Chase et al, 2002; Lam et al, 2002). They are designed specifically to test the effectiveness of the heavy derivative control methods and to verify the simulations and design that led to them. The trials are conducted on ICU patients since they represent a highly controlled test group who often experience elevated blood glucose levels. Additionally, tight glucose control has been shown to reduce ICU patient mortality by as much as 45%, which is an added benefit of tight glucose regulation for this subject group (Van den Berghe et al, 2001).

Qualifying patients had to be stable, have elevated blood glucose levels over 8 mmol/L, have an arterial line and a nasogastric feed, and be expected to remain in the ICU for at least three days. In addition, patients with morbid obesity ( $BMI > 35\text{kg/m}^2$ ) or neuromuscular blockade were not considered. The Canterbury Ethics Committee granted ethics approval for these trials.

The clinical trials are a two-day procedure for each participant. The first day of the trial measures the uncontrolled glucose regulatory system response and the second day implements active insulin control of the glucose regulatory system response using the heavy derivative control algorithm.

### 2.1 Clinical Trial Day One:

The trial begins at 0700 hours at which time the patient is fasted for four hours. Blood glucose readings are taken every hour to determine a basal blood glucose level. At 1100 hours, blood is taken for C-peptide and blood insulin tests to screen for insulin contamination and determine the basal insulin level, respectively. The patient is then given a 75g oral glucose tolerance test (OGTT) glucose dose via the nasogastric tube. Plasma glucose is measured at 15-minute intervals until 1500 hours. Paired samples are taken, with one analysed using a bedside *Glucocard<sup>TM</sup> Test Strip 2* glucose testing kit and the other sent to the laboratory for comparison. The error in the absolute readings are approximately 7% for the *Glucocard<sup>TM</sup> Test Strip 2* tests, and 3% for the laboratory tests at typical elevated blood glucose levels (Phillips et al, 1994; Peters et al, 1996).

### 2.2 Clinical Trial Day Two:

The procedure is repeated as per day one, however short acting soluble insulin with 0.2U/ml in 0.9% saline is infused via an intravenous cannula using a Graseby 3500 syringe pump. Plasma glucose is measured at 15-minute intervals as previously and the insulin infusion rate is manually adjusted every 15 minutes according to the heavy derivative control algorithm. This approach is designed to specifically test the algorithm and eliminate the impact of any specific equipment.

## 3. MATHEMATICAL MODELLING

To implement tight glucose control using an automated insulin infusion system for patients in an intensive care unit (ICU) requires a model of the glucose regulatory system that accounts for intravenous infusion of exogenous insulin. The initial physiologically verified model employed originated from the work of Bergman et al. (1985), utilizing the concept of a remote compartment for the transport of

insulin between the subcutaneous infusion site and its utilization to reduce blood glucose levels.

Intensive care unit (ICU) patients have direct arterial/venous lines that bypass the subcutaneous compartment in the three compartment model, and require only two compartments. The first compartment models insulin uptake into the blood, and the second models blood glucose level and insulin mediated transport of glucose from the blood. The model is defined:

$$\dot{G} = -p_1 G - p_4 I (G + G_B) + P(t) \quad (1)$$

$$\dot{I} = -n(I + I_B) + u(t) / V_I \quad (2)$$

Where  $G$  is the blood glucose level over basal level  $G_B$ ,  $I$  is the insulin level over basal level  $I_B$ ,  $u(t)$  is the exogenous insulin infusion,  $P(t)$  is the exogenous glucose input,  $n$  is a time constant for the insulin, and  $p_1$  and  $p_4$  are patient dependant parameters. Currently,  $p_4$  is a time constant that couples the blood insulin level to the rate of glucose utilization by the body, representing the simplest possible dynamic between these two compartments.

Additional model dynamics linking the two compartments in Equations (1) and (2) may be needed, however, any missing dynamics are small enough to have negligible effect on the ability to derive an appropriate controller. More specifically, the upward rise of glucose concentration in the blood in this model does not depend on  $p_4$ , and it is this rise that the heavy derivative control focuses on limiting.

The model is therefore patient specific and is adapted to each person before a controller is developed. In the longer term, average parameter sets will be identified from extended clinical trials that are in development. Such parameters, if they can be identified for different types of patient would eliminate a great deal of customisation.

Hence, current controller design is accomplished in three steps. First data from an uncontrolled oral glucose tolerance test (OGTT) is gathered from the patient. Secondly, the patient specific parameters,  $p_1$  and  $p_4$ , are obtained using unconstrained optimisation designed to minimise the difference between modelled and test behaviour. Finally, given a model that fits the error bounds of the uncontrolled patient data, control gains are developed using a second unconstrained optimisation to find derivative weighted gains that minimise the magnitude and duration of blood glucose excursion from the patient's basal level for the same OGTT input.

The first step in the process is to fit a continuous function to the patient's uncontrolled, day one, OGTT data using a log-normal function, which tends to match such data quite well [8], to derive a function,  $G_{patient}$ , which can be discretised for optimisation into

a series of time points,  $\bar{G}_{patient}$ . Changing the values of  $p_1$  and  $p_4$  will change the model output, so that a similar series,  $\bar{G}_{model}$ , matches the continuous function approximated by  $\bar{G}_{patient}$ . Unconstrained optimisation can accomplish this error minimisation task using an objective function defined:

$$R = (\bar{G}_{model} - \bar{G}_{patient})^T (\bar{G}_{model} - \bar{G}_{patient}) + e^{-p_1 C} + e^{-p_4 C} \quad (3)$$

Where  $C$  is a large positive constant, defined to ensure that  $p_1$  and  $p_4$  remain positive and therefore valid as parameters in the model. By changing the discretisation, certain points in the model solution and the continuous function  $G_{patient}$  can be constrained to match more accurately. Typically, several extra time points around the peak of the glucose response curve are added to ensure the rise and inflection of the glucose curve are adequately captured. It is this rise and inflection that are critical to effective derivative weighted control, as it is this portion of the curve that instigates the vast majority of the control, and hence insulin, infusion input.

The total amount of glucose infused simulating an OGTT is 34 mmol/L, a value obtained by converting 75g of glucose and assuming the patient has the glucose evenly distributed in a 12L fluid volume (Furler et al, 1985; Bergman et al, 1985). To account for the different rates of uptake, the peak of the simulated exogenous glucose infusion profile,  $P(t)$ , is set at approximately 80% of the time required for the patient's uncontrolled OGTT peak glucose reading, and modelled as a continuous lognormal function. Hence, the simulated and actual uptake rates for uncontrolled OGTT will be similar and the total glucose input will be identical.

The controller determines the amount of exogenous insulin,  $u(t)$ , infused. The model is set to run with a 15 minute sampling interval to match the clinical trial program developed. A heavy derivative proportional-derivative (PD) controller is employed:

$$u(t) = U_0 * (1 + K_p * (G + G_{prime}) + K_d * dG/dt) \quad (4)$$

$$G_{prime} = G_b - G_t \quad (5)$$

Where  $U_0$  is the basal insulin infusion rate,  $K_p$  is the proportional gain and  $K_d$  the much larger derivative gain (Lam et al, 2002). More specifically, the proportional gain is typically 20-50x smaller than the derivative gain.  $G_{prime}$  is an offset term to the proportional control. A patient with a high basal glucose level,  $G_b$ , can have their glucose level controlled to a lower target blood glucose level,  $G_t$ , by increasing  $G_{prime}$ , which is the difference between the target blood glucose level ( $G_t$ ) and the actual, elevated basal blood glucose level ( $G_b$ ) for the patient. The more positive  $G_{prime}$  is the greater the

proportional feedback term by setting the target basal level below the actual (elevated) basal level.

The control gains are determined by minimising the objective function ( $R$ ) defined:

$$R = C_1 [G(\tilde{t}) - G_t]^T [G(\tilde{t}) - G_t] + C_2 \dot{G}(\tilde{t})^T \dot{G}(\tilde{t}) + e^{-K_d C} + e^{-K_p C} \quad (6)$$

where  $C_1$ ,  $C_2$  and  $C$  are positive constants that can be suitably modified to obtain the desired results. The  $G(\tilde{t})$  terms in the objective function minimise the area between the blood glucose levels,  $G(\tilde{t})$ , from the measured data and the target blood glucose levels,  $G_t$ . The  $\dot{G}(\tilde{t})$  terms in the objective function minimise the slope of the output glucose levels, reducing oscillation in the blood glucose response curve, a problem that can occur if the gains are too large. The exponential terms in the objective function ensure  $K_d$  and  $K_p$  are positive, providing the basis for a practicable solution. Overall, optimisation is employed not to find a best solution but to efficiently search a large domain of possible control gains.

#### 4. CLINICAL RESULTS

Initial proof of concept clinical trials were performed on two ICU patients. Following consent being obtained, each patient was subjected to the two day trial defined. While initial patients are tested with patient specific models, later patients will employ average parameters based on extended trials being developed.

Patient 1 was a 67 year old female subject in the ICU for three days suffering from kidney failure. The kidneys can remove up to 30% of effective insulin, so kidney failure is an “insulin sparing” condition that can lead to a flatter glucose response (Charpentier et al, 2000). The patient's basal insulin level of 70 pmol/L was slightly high and the patient was therefore both hyperglycaemic and somewhat hyper-insulinaemic as well.

Figure 1 shows the measured and model predicted glucose response for day one (uncontrolled) and day two (controlled). The measured data is presented with the 7% error associated with GlucoCard™ 2 measurements. The magnitude and duration of blood glucose excursion from the basal level are reduced by at least 50%. The target sub-basal glucose level of 5.5mmol/L was not fully reached, as the derivative control was not effective as the tail of the glucose response curve flattens off. This failure is an example of the need for gain scheduling or a modified control approach in this flatter response regime. Note also that the uncontrolled response is relatively flat for an OGTT, which is a result of the patient's relative hyper-insulinaemia resulting, at least in part, from kidney failure.

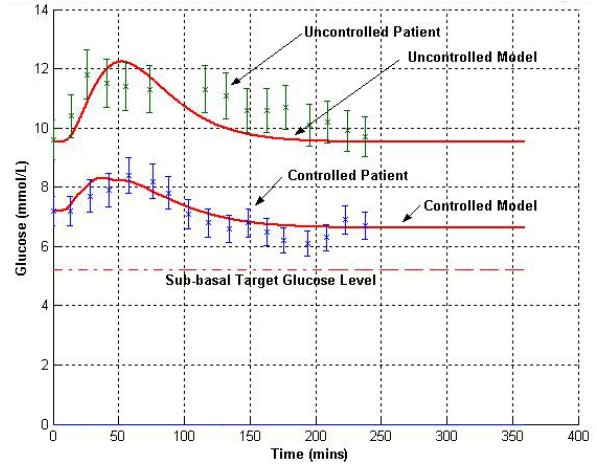


Fig. 1: Patient 1 OGTT Response

Overall, the automated algorithm provided rapid, effective control of the OGTT input and the simulated controlled response was an extremely good match for the measured data, as seen in Figure 1. The difference in day one and day two basal levels is primarily due to changes in feeding and insulin administration over the night between the OGTTs. Finally, the patient's blood glucose concentration began to increase steadily back to 10 mmol/L after the controlled day two test when hospital staff returned to their sliding scale protocol showing the need for, and effectiveness of, automated methods for tight glucose regulation.

Patient 2 was a 75 year old male in the ICU for 2 days suffering from a significant head injury. Uncontrolled patient data from day one, as shown in Figure 2, showed the patient behaves as a Type 1 diabetic. The extremely high glucose levels and almost permanent period of excursion from the basal glucose level are similar to a Type 1 diabetic OGTT response, however available records did not show such a diagnosis. Laboratory tests for insulin level confirmed the assumption of essentially Type 1 diabetic behaviour with a very low insulin level of 3pmol/L.

The controlled response in Figure 2 shows the need for an additional insulin accumulation dynamic in the model, with the dip in glucose response at 180 minutes. The controlled simulation does not capture this dip, or the initial stronger rise, illustrating how the simple coupling dynamic in Equation (1), utilizing the parameter  $p_4$  is not fully adequate. The actual results indicate that some insulin input accumulates in a second compartment before utilization.

Approximating this dynamic by adding a 75 minute delay on a portion of the insulin infusion resulted in a curve more closely aligned with the controlled patient data in Figure 2. This approximation delays the onset of some of the infused insulin much as an

accumulation in a secondary compartment would. The results confirm the need for this accumulator dynamic.

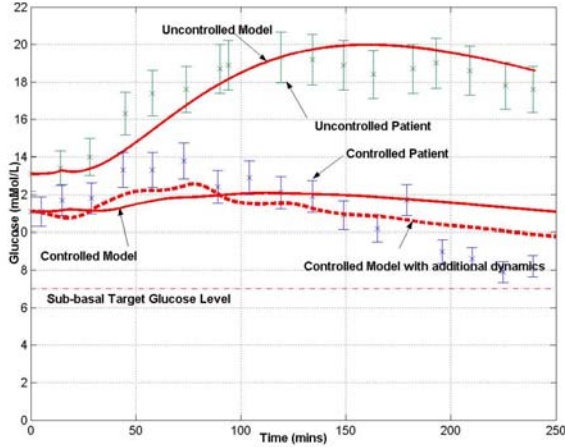


Fig. 2: Patient 2 OGTT Response

The overall performance of the controller was still quite effective. The peak blood glucose excursion is reduced 60% and the duration was cut to two hours from the much greater than four hour excursion that would have resulted in the uncontrolled case. Finally, the eventual final basal level was reduced approximately 3mmol/L from the starting value for that day.

Comparisons between the predicted and actual insulin infusion profiles for day two of the trials were made as a means for determining the effectiveness of the modelling methods. Table 1 shows that the total insulin infused differed from the predicted total by no more than 8%. One cause for difference is the 0.2 U/mmol discrete insulin infusion step available versus the exact analog values used in the simulation, and a tendency to round down to the nearest discrete infusion level during the trials as a conservative choice. The excellent match between predicted, or simulated, insulin usage and the actual insulin employed verifies the physiological accuracy of the models and methods employed.

Table 1: Comparison between predicted insulin and trial insulin infused

Patient	Predicted Insulin (Units)	Actual Insulin (Units)	Difference (%)
1	4.50	4.43	- 1.55
2	4.90	4.50	- 8.16

Blood glucose excursion and control efficacy may be best measured by comparing the area reduction in the glucose response curve and change in basal glucose value, as shown in Figure 3. The ratio of the two areas in the figure is a measure of how much the glucose excursion is reduced, while basal level reduction shows the effectiveness in reducing elevated levels. Table 2 summarises these values for

both patients, with reductions of around 80% blood glucose excursion in area and 15-19% in basal level, versus the uncontrolled case.

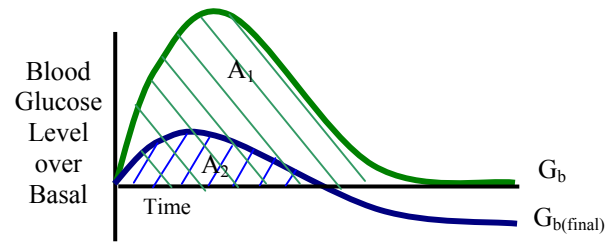


Fig. 3: Measures of Blood Glucose Excursion

Table 2: Comparison of Glucose Excursion Data

	Day One	Day Two	Ratios			
	$G_b$	$A_1$	$A_2$	$G_b$ Final	$G_b$ Ratio	$A_2/A_1$
1	9.6	292	60	6.1	0.85	0.21
2	13.1	1082	196	7.9	0.71	0.18

Finally, the accumulator dynamic noted in the clinical results has three potential causes. First, is the physiological battle between the body's desire to return to the (elevated) basal level and the controller's attempts to hold it down, as best seen in Figure 1. Second, is the demand for insulin in the blood is secondary to those of the brain and liver, leading to the possibility that meeting these demands first causes a reduction in useful insulin in the blood and a later over reaction. Finally, it is believed that insulopenic, or very low insulin level, patients can develop lipo-toxicity, suppressing insulin release from any active beta cells. Therefore, when exogenous insulin is infused these beta cells are free to release endogenous insulin not initially accounted for (Del Prato et al, 2002). Further tests will help clarify the specific causes of this dynamic, and improve the models and clinical trial methods employed.

## 5. CONCLUSIONS

These trials, are to the best of the authors' knowledge, the first human clinical trials of feedback controlled active insulin infusion and have been completed with very good success. The research has succeeded in the creation and validation of an intravenous insulin infusion model, and in demonstrating tight actively controlled blood glucose level regulation for the first time. The heavy derivative control approach employed has been demonstrated to be as highly effective in practice as in simulation, with reduction in glucose excursion of up to 82% and basal glucose reduction of up to 19%.

The two trials have shown a high level of correlation between the simulation model and the patient results.

This strong correlation certifies the physiological validity of the models and methods employed. In particular, the model's ability to capture the insulin usage to within 10% of actual values validates the fundamental assumptions made. However, the results have clearly demonstrated the need for additional accumulation dynamics in the intravenous glucose regulatory system model, and the need for gain scheduling or a two-stage controller to bring glucose levels back to a set basal value as derivative values become negligible in the tail of the OGTT response.

Finally, two simple measures for capturing the effectiveness of automated glucose regulation are introduced. The comparison of blood glucose excursion area, for a given input, is seen to capture the essential details of the magnitude and duration of the blood glucose excursion from the patient's basal level. Secondly, many diabetic individuals have elevated basal blood glucose levels so that comparing the final basal value that the controller achieves is a simple measure of the controller's ability to "fight physiology" and reduce blood glucose below the basal level.

Future developments include advancements in patient simulation models and improvements in the control systems employed. Particular areas of work include improved optimisation methods for determining patient specific parameters and control gains, and further trials on ambulatory patients using subcutaneous insulin infusion. The ultimate goal is consistent, robust automated blood glucose control.

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